Quality by Design in the New Pharmaceutical Quality Assessment System (PQAS)

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Outline

- An FDA Perspective on Current CMC Submission and Review Practices
- Pharmaceutical Quality Assessment System (PQAS)
  - CMC pilot program
- Setting Specification in QbD Paradigm
- QbD - Drug Release Rate (ACPS, October 2005)
- Regulatory Flexibility
- Conclusions

Current CMC Submission and Review Practices

- Submissions
  - Focus more on data and format and less on critical analysis and scientific justification/rationale
  - Often contain insufficient pharmaceutical development information
  - Contain voluminous data that is not always presented in a comprehensive or scientific manner
  - Concentrate mostly on chemistry and product specifications but less on manufacturing science
  - Reflect apprehension on what to share with FDA

Current CMC Submission and Review Practices

- Review
  - Resource intensive
  - Need to identify relevant data in submission prior to analysis and critical assessment
  - Guidance based
  - Focuses on establishment of specifications
- Regulatory Process
  - Generally not friendly and communication not always timely
  - Insufficient direct dialogue between FDA and applicant scientists
  - Doesn’t allow for timely discussion and dispute resolution
  - Lack of desired coordination and inconsistencies may exist among review divisions and field districts

Current CMC Submission and Review Practices

- When NDA is approved
  - Everything submitted in the application is locked in
  - There is no need to identify critical CMC elements (i.e. CQAs and CPPs) at time of approval
- The consequences are:
  - Reluctance to share relevant scientific information with FDA
  - Many unnecessary supplements because every change could be considered “critical”

Process Validation

- Focuses primarily on the “3 batch” concept
  - Using the “best” – talent, day shift, same lot of raw materials, etc.
  - Is this representative of routine production operations?
  - Does this consistently ensure a “state of control”?
  - Sets up the mind set – “do not rock the boat” - the product is approved and its process validated!
  - Continuous improvement is difficult
  - Low efficiency is locked in!

Pharmaceutical Quality Assessment System (PQAS)

- Based on scientific knowledge and understanding of product and process by applying quality-by-design principles
- **Objective (To implement QbD)**
  - To facilitate innovation and continuous improvement throughout the product lifecycle
  - To provide regulatory flexibility for specification setting and post-approval changes
  - To streamline the submission and review processes

PQAS - What does it mean?

- In a QbD paradigm, process understanding links manufacturing controls to CQAs/specifications and hence to the desired performance of the DP
- In the desired state, quality control is moved upstream to critical process steps and CPPs rather than relying on end-product testing
- To achieve this desired state, relevant design information is necessary for quality assessment
- It is imperative to define CQAs through multi-disciplinary interactions, e.g., clinical, pharm/tox

PQAS – Submissions

- Streamline the submissions
  - No need to submit irrelevant, redundant, or unorganized data
  - Need to submit relevant scientific information and analysis (e.g., summaries, tables and graphs)
- PD Information
- Comprehensive QOS, possibly as the “main” review document
  - Good start in ICH (Chicago, November 2005)
- Relevant product and manufacturing process design information
- Applicants’ assessment prior to submission

PQAS– Assessment

- To ensure, through scientific assessment of applications, that necessary quality attributes are built in (QbD) and the drug product can be manufactured consistently with high quality for its intended use (i.e. safety and efficacy)
- CMC review is not:
  - Only about setting product specifications
  - Conducted in isolation (without clinical relevance)
  - To tell the applicant how to develop or manufacture its product

PQAS– Assessment

- Assesses PD to understand how the applicant designed and developed its product and process
- Identifies CQAs (e.g., physical/chemical properties) of DP, DS, and excipients based on DP quality, performance, stability, and manufacturability requirements
- Evaluates suitability of formulation
- Assesses appropriateness of process design
  - Evaluates scientific rationale used to support the selection of CPPs and in-process controls
  - Links material properties and critical steps to CQAs of DS, DP and intermediates

CMC Pilot Program

- Goals:
  - To implement QbD
  - To evaluate elements of the new PQAS
  - To enable the public and industry to provide feedback to assist FDA in developing a guidance on the new quality assessment system
  - To establish appropriate metrics to evaluate quality of both submission and assessment
- Program target dates
  - Request to participate - March 31, 2006
  - NDA or sNDA submission – March 31, 2007

Process of CMC Pilot Program

- Potential participants will discuss plans with ONDQA
- Once accepted, participants can meet with ONDQA as frequently as needed
- Assessment will be conducted by a team of experienced reviewers with good understanding of the new PQAS and strong background in PD and manufacturing processes
- Team Review
- Participation of ORA and CDER's compliance (Review – Inspection Team, PAT Model)

CMC Pilot Program – Status Report

- FDA Focus
  - Public Health Protection
  - Good Science
  - Efficient process
- Strong interest in the pilot
  - Avenue to share information
  - Flexible review process
  - Review – Inspection Team Model
- Reluctance to challenge FDA's regulatory system
  - Not gaining full benefits
  - Traditional proposals for specifications
- FDA is changing while industry is waiting!

Setting Specification in QbD Paradigm

- The Desired State
  - Product quality and performance should be achieved and assured by design of effective/robust manufacturing process (QbD)
  - Product specification should be based on mechanistic understanding of how formulation and process factors impact product performance
  - Product quality and performance linked to clinical safety and efficacy

Setting Specification in QbD Paradigm

- Clinical Relevance
  - Product quality is the foundation upon which clinical safety and efficacy assessment and decisions depend
  - Integration of CMC and clinical assessment (FDA Model)
  - Need to establish appropriate, preferably quantitative, correlation between quality attributes and clinical performance (safety and efficacy)
    - Clinical trial design including dose ranging studies
    - Biomarkers
    - Modeling
- PQRI – FDA Specification Workshop, March 2005

Setting Specification in QbD Paradigm

- Value of QbD Approach
  - Drug Release/Dissolution Testing (ACPS, October 25, 2005)
  - Scope: IR solid oral dosage form

Utilities of Dissolution Testing

- To guide drug development to select formulations for further in vivo studies
- To evaluate comparability between products before and after changes in formulation and/or manufacturing
- To serve as surrogate for in vivo bioequivalence (IVIVC) and/or as justified per Biopharmaceutics Classification System (BCS)
- To be used as a quality control tool to ensure batch-to-batch consistency of product performance

Current System - Deficiencies

- Empirical approach to setting specification to fit the available data
- Clinical linkage (safety and efficacy) not always assured
- Negotiation to set specification because of limited data, and lack of systematic scientific approach to product development
- Specifications may not be reflective of the “true” product quality
- Out of specification (OOS) results leading to:
  - Non-compliance and subsequent investigations
  - Product quarantine/delays or recall from the market depending upon the situation
  - Drug shortage in the market in certain cases
- Regulatory hurdle for continuous improvement

Current System - Challenges

- Is empirical approach to setting dissolution specification appropriate?
  - Non-statistical sample size
  - Limited data
  - Absolute Q values (based on mean but without SD)
  - Lack of adequate product/process understanding
- Is dissolution a suitable indicator (sensitive and discriminating test) of product performance for all relevant dosage forms?
  - Highly soluble and highly permeable drug products
  - Potent and/or narrow therapeutic index drug products with low solubility
  - Addressing post-approval manufacturing changes to demonstrate equivalence to the approved drug product

Current System - Challenges

- Can disintegration or some other quality attribute substitute dissolution?
  - Under what circumstances?
- Are there any circumstances/cases for which dissolution and/or disintegration testing may no longer be needed at release?
  - How to assure product quality/performance for such DPs throughout their intended shelf-life?

Current System - Challenges

- Poor understanding of observed variability
  - Product related variability
    - Formulation components
    - Manufacturing process
    - Operator
  - Measurement system variability
    - Analytical methods (e.g., USP calibrator tablet)
    - Dissolution apparatus
    - Operator

Current System - Challenges

- Drug development efforts with poor or lack of understanding:
  - Raw material properties
  - Effect of formulation components' properties on manufacturing processes (unit operations)
  - Effect of manufacturing process on the critical quality attributes of the drug product
  - Causal link between critical material attributes of formulation components (API, excipients) and critical quality attributes of the drug product
  - Associated risk(s) to product quality

QbD - Drug Release Rate

- Drug release specifications should be defined to deliver the desired performance (intended use) of a proposed product in the intended patient population
- Design the product and manufacturing process to meet the intended and desired specifications
- The intended specifications should be
  - Proposed and established early in drug development
  - Guided by information obtained from pre-clinical and pre-formulation drug characterization
- Understanding the sources of variability and measuring and controlling critical material attributes (raw and in-process materials) as a means for process control
- For some conventional dosage forms, prior knowledge could facilitate
  - Design of drug product and manufacturing process
  - Establishment of desired dissolution specifications

The Logic of QbD*

- Once a formulation scientist understands the patient's requirements, they can design a formulation using either or both approaches:
  - Prior knowledge: choose API form, excipients and processes that will achieve the expected release profile
  - QBD: select API form, excipients and processes that have greatest impact on quality attributes that affect release of drug
    - Selections based on theoretical/fundamental understanding, alternative measurements and heuristic development
  - * PhRMA Presentation, ACPS, October 25, 2005

Connecting QbD to Quality Attributes*

QBD Factors ↓	Porosity	Hardness	Wetting	Swelling/ Penetration	API Solubilization
DP Excipient Selection	PS of excipients (match to API) Hardness/ Brittleness of excipients Granule strength	Bonding Index Brittle Fracture Index Compression force profile via simulation Other mechanical properties	Contact angle measurements	Solubility of excipients Microscopic evaluation of swellability	Analysis described in porosity, wetting and swelling
DP Process Selection*	1st choice: wet granulation 2nd choice: dry granulation 3rd: direct comp.	1st choice: dry granulation 2nd choice: wet granulation/direct compression	1st choice: wet granulation 2nd choice: direct comp. 3rd: dry granulation	1st choice: wet granulation 2nd choice: direct comp. 3rd: dry granulation	1st choice: wet granulation 2nd choice: direct comp. 3rd: dry granulation
API Form Selection	PS of API (match to excipients) Hardness/ Brittleness of API	Bonding Index Brittle Fracture Index Compression force profile via simulation Other mechanical properties	Contact angle measurements	Counter ion selection Polymorph selection Solubility of API form Microscopic evaluation of swellability	Counter ion selection Polymorph selection Analysis described in porosity, wetting and swelling
API Process Selection	N/A	Crystallization/ Milling – mechanical property; shape/size	Milling	N/A	Crystallization/ Milling – shape/size

* PhRMA Presentation, ACPS, October 25, 2005

Real Time Release (RTR)

- Ability to evaluate and ensure acceptable quality of in-process and/or final product based on process data, which includes valid combination of
  - Assessment of material attributes by direct and/or indirect process measurements,
  - Assessment of critical process parameters and their effect on in-process material attributes
  - Process controls
- Combined process measurements and other test data generated during manufacturing can serve as the basis for real time release of the final product
- Thus, demonstrate that each batch conforms to established quality attributes

Basis of RTR for Dissolution

- Reliable prediction of dissolution:
  - Accurate measurement of one or more in-process attributes, that are critical and impact dissolution
    - Relationship must be established and demonstrated
  - Monitoring and control of the processes and associated process parameters
  - Controlling relevant attributes of formulation components that have direct/indirect impact on dissolution
  - Measurement and sampling strategy
    - Continuous measurements (in-line, on-line, at-line)
    - Representative statistical sampling
- Dissolution is an outcome of a complex multivariate processes/ factors

Multivariate Processes/Factors

- Materials
  - Chemical and physical attributes for incoming batch, e.g., real time measurements for moisture and PS and correlate to downstream process parameters
- Granulation
  - Process parameters, material attributes
- Drying
  - Process parameters, e.g., air inlet/outlet and bed temperatures
  - Material attributes, e.g., moisture content
  - Establish correlation between real-time moisture content and product bed temperature for consistent drying

Multivariate Processes/Factors

- Blending
  - Material attributes, (DS, disintegrant and lubricant)
    - BU as predictive attribute of CU and dissolution
- Compression
  - Process attributes, e.g., force
  - Material attributes, e.g., hardness, CU
- Coating
  - Material attributes, e.g., relationship of moisture content between uncoated and coated tablets

QbD - Drug Release Rate Summary

- In a QbD paradigm, relevant design information must be included in CMC submissions
- The controls of critical variables such as drug particle size may be more relevant in assuring quality, for some drug products, than a dissolution test
- ICH Q8 will facilitate the implementation of QbD and enhance utility of many aspects of ICH Q6A

Regulatory Flexibility

- Can be considered based on product and process understanding (QbD) in submission
- Pre-marketing:
  - Faster review
  - Higher probability for first cycle approval
  - Flexibility in setting specifications (within the design space)
- Post-marketing
  - Opportunities to update and/or modify the design space (e.g. comparability protocols)
  - Facilitates innovation and continuous improvement
  - Potential reduction and/or elimination of certain type of supplements

Conclusions

- ONDQA is moving forward with the implementation of PQAS
- FDA is striving for an international harmonized approach (ICH)
- FDA will continue to seek industry input and collaboration
- Regulatory flexibility is predicated on meaningful improvements to pharmaceutical development and scientific information submitted in application
- Today's system may continue to exist
- Today's challenges must be addressed
- Focus remains on availability of safe, effective and high quality pharmaceuticals